Remarks

The Applicants have amended the Specification to correct a typographical error. Entry of the change into the official file is respectfully requested.

The Applicants acknowledge that Claims 10-13 have been withdrawn from further prosecution. Those claims have been cancelled without prejudice and without disclaimer of the subject matter therein. The Applicants specifically reserve the right to file one or more divisional applications directed to the subject matter of those claims.

Claims 14 and 15 have been added. They recite that the prosthesis is a shunt and a coronary stent, respectively. Support may be found in original Claim 1, for example. Entry into the official file is respectfully requested.

All of Claims 1-9 have been amended to place them into better condition for allowance. A number of the claims have further been amended for the reasons set forth below.

Claims 1-9 stand rejected under 35 USC §112 as being indefinite. The Applicants note with appreciation the Examiner's helpful comments with respect to Claims 1, 3, 4, 8 and 9. Those claims have been amended accordingly. For example, Claim 1 has been amended to remove the "a stent or shunt" language. Claim 3 has been amended to remove the "coronary stent" language. Claim 4 has been amended to characterize the wire or hollow wire as being alternatives. Claims 8 and 9 have been amended to remove the preferred ranges. Withdrawal of the §112 rejection is respectfully requested.

Claims 1-5 and 7 stand rejected under 35 USC §102 as being anticipated by Kaplan. The Applicants respectfully submit, however, that there are significant differences between Kaplan and those rejected claims. Reasons are set forth below detail.

Kaplan relates to a method for inhibiting restenosis in a recanalized blood vessel, whereby an antioxidant substance is delivered to a target site (e.g. Kaplan, claim 1). Kaplan provides a list of different possible antioxidants, for example, on page 6, lines 11 to 19, and states that the antioxidant is preferably probucol. However, Kaplan provides no examples illustrating how to inhibit restenosis or any data concerning the efficacy of the listed antioxidants, even probucol. Kaplan is entirely speculative. One skilled in the art would be left in doubt as to which antioxidants worked, if any, the expected degree of shrinkage or inhibition achieved, and the suitable time/dosage data. Therefore, Kaplan is not sufficiently disclosed to be enabling. It cites no examples, either real or theoretical. It is purely speculative and is not considered valid prior art for the assessment of anticipation.

Furthermore, dosage concentrations in Kaplan are expressed in "mass per kg of body weight" (e.g. Kaplan, claim 2). The use of such units in Kaplan indicates the device is intended for use with an infusion catheter, which provides a partly systemic administration route. While that systemic route is elaborated, Kaplan provides no enablement for a prosthesis which is non-systemic, and requires dosage expressed in "mass per mm^2 prosthesis area." Consequently, Kaplan only describes how to administer using an infusion catheter, but does not instruct those skilled in the art how to prepare a prosthesis provided with melatonin. Given the absence of any guidance, examples or any preferred embodiments regarding the subject matter of Claim 1, Kaplan is inapplicable to Claim 1 under §102.

It is also noted that Kaplan concerns the treatment of restenosis (e.g. Kaplan, page 5, lines 2 to 7). This condition is different from the claimed modification of the healing response after implantation of a prosthesis. The former involves a systemic administration as mentioned above, and concerns shrinkage of a cell mass formed due to injury by recanalization. This

contrasts with Claim 1 which avoids cellular proliferation concurrent with widening a vessel by changing the healing response.

Delivery in Claim 1 by the claimed prosthesis impregnates the injured vessel wall with melatonin, allowing scavenging of free radicals that originate from white blood cells involved in the initiated by the injury-initiated inflammation process. Furthermore, a direct effect on the smooth muscle cells inhibits their proliferation. The combination of an effect on the induction of the healing cascade (scavenging of free radicals) and the direct effect on smooth muscle cells results in a faster, more complete healing, an accompanying expedient restoration of the endothelial layer, and a faster control of the inflammatory process. In turn, this provides less stimuli to activate further smooth muscle cell proliferation. Moreover, the direct inhibitory effect on the smooth muscle cell proliferation results in an improved physiological restoration of the vessel anatomy.

These therapeutic effects provide a modification of the healing after a specific prosthesis-mediated vessel wall injury, resulting in a faster and improved physiological healing. In Kaplan, in sharp contrast, no such effects are attributable to melatonin. Merely the inhibition of restenosis is described. Probucol, exemplified in Kaplan, also does not mention this combination of effects, and has never been shown to have an influence on healing. As a consequence, Kaplan is not enabled and does not mention the therapeutic application of Claim 1. Claim 1 is not anticipated by Kaplan. Withdrawal of the rejection of Claims 1-5 and 7 under §102 over Kaplan is respectfully requested.

Claim 6 stands rejected under 35 USC §103 over the hypothetical combination of Shanley with Kaplan. Claims 8-9 stand rejected under 35 USC §103 over Kaplan taken alone.

The Applicants respectfully submit that both rejections are inapplicable for the reasons set forth below.

Stent-delivered melatonin has an effect on healing after implantation of a prosthesis, which reduces tissue injury. Melatonin scavenges oxygen-free radicals released by inflammatory cells, thereby reducing injury and inflammation induced by the vascular wall injury. Melatonin also has a balanced direct inhibitory effect on the smooth muscle cells preventing exaggerated smooth muscle cell proliferation and in-prosthesis tissue in-growth. These findings are taught by the Applicants, for example, on pages 14 to 20 of their Specification as originally filed.

Kaplan does not disclose, teach or suggest these properties of melatonin since Kaplan describes only an unsupported inhibition of restenosis. Probucol cited in a preferred embodiment of Kaplan does not have a anti-proliferative effect on smooth muscle cells. There are no demonstrative examples, and the Applicants' own experiments confirm that probucol has no effect on neointimal hyperplasia (this application, page 19, line 25 to page 26, line 4 as originally filed). One skilled in the art, understanding the impotence of probucol, would not try to use other compounds such as listed on page 6, lines 5 to 18, that are implicated with the same ineffectiveness.

In sharp contrast, prosthesis-delivered melatonin exhibits a significant effect on different targets of the healing cascade by scavenging oxygen-free radicals. It also shows direct anti-inflammatory effects and direct anti-proliferative effects on smooth muscle cells, resulting in an improved physiological healing (present application, page 19, lines 25 to page 26, line 14).

Moreover, as noted above, delivery in Kaplan is primarily directed to a partly systemic route of administration which does not provide the healing effects of Claims 6, 8 and 9 gained by

impregnation using a prosthesis. Kaplan does not suggest any difference of effect attributable to these modes of delivery.

The Applicants therefore respectfully submit that even if one skilled in the art were to hypothetically combine Shanley with Kaplan, the result of that combination would still fail to disclose, teach or suggest the subject matter of Claim 6. Similarly, the Applicants respectfully submit that Kaplan is inapplicable to Claims 8 and 9 for the reasons set forth above. Withdrawal of both rejections is respectfully requested.

In light of the foregoing, the Applicants respectfully submit that the entire Application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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